certainly not to any method which could possibly achieve these desirable results.

Claims 84 and 86-92 have now been rejected as being unpatentable over Müller *et al.* in view of Buyske under 35 U.S.C. § 103(a). The Examiner now contends that Müller *et al.* teaches a transdermal product comprising an acrylate base, and in particular polymers comprising a functionalizing monomer, a C_4-C_{12} acrylate, and a C_1-C_4 acrylate. Neural therapeutics are said to be specified, and cross-linking agents are disclosed. Buyske is said to teach deprenyl (*i.e.*, selegiline) for treating Parkinson's disease, and to specifically mention transdermal delivery. The Examiner thus concludes that it would be obvious to add deprenyl to the composition of Müller *et al.* to achieve the beneficial effect of treating Parkinson's disease in view of Buyske. The claimed method of making is said not to be considered to be a patentable limitation in composition claims during prosecution. This rejection is respectfully traversed in view of the above arguments and for the further reasons set forth hereinafter.

The Müller *et al.* reference, which was recently cited by applicants, is specifically directed to transdermal products which include a basic active component, permeable, pressure-sensitive adhesive polymer material. In the background discussion set forth in the Müller *et al.* specification, it is noted that using basic active component reservoirs with hydrophilic swellable polymers is known, but does not always lead to satisfactory results. Thus, to improve upon this prior art, these patentees state that they have developed a novel pressure-sensitive adhesive polymer using basic monomers, which allows for improved delivery of basic active components, particularly through the lipophilic barrier of the human cornea. Therefore, the critical element of the invention in Müller *et al.* is the modification of pressure-sensitive adhesive

polymer materials, including acrylic adhesives, so as to incorporate basic monomers, in particular amino esters with acrylic and/or methacrylic acid or other olefins, thereinto. Thus, the basicity and quantity of these basic monomers which are polymerized into the adhesive are said to establish a chemical equilibrium to establish the proportion of active component which is present as a free base in the system.

The preferred adhesives for use in connection with Müller *et al.* are polyacrylate-based adhesives, although these are said not to restrict the nature of Müller *et al.*'s invention. Specific monomers which are said to provide the basic characteristics required by this patent are listed at column 4, lines 32 *et seq.* of Müller *et al.*

Firstly, all of the pending claims in this application are specifically directed to a transdermal delivery system consisting essentially of a blend including one or more hydrophobic acrylic polymers. The requirement in Müller *et al.* for inclusion of basic monomers, which are primarily nitrogen-containing monomers, and the polymerization of the polyacrylate-based adhesives thereof, ensures that the transdermal product thereof does not and could not possibly meet the limitations of applicants' claims, and cannot consist essentially of a hydrophobic acrylic polymer. The requirement for the addition of nitrogen-containing basic polymers in the polymerized product thereof clearly adds polarity and hydrophilicity thereto. In support of this assertion, the Examiner's attention is directed to the enclosed Declaration of Dr. Gordon Flynn, a renowned expert in this field. Dr. Flynn, who has been an expert in the field of transdermal drug delivery for almost 40 years, including his participation reviewing grants for the National Institutes of Health and as a consultant to the FDA, explains the nature of the disclosure in Müller *et al.* Dr. Flynn thus explains that Müller *et al.* is concerned with the use of

adhesive polymer materials in transdermal systems which can effectuate the delivery of basic active components. This is said to be accomplished by incorporating monomers with a basic (amine) character thereinto. Müller *et al.* thus requires one to utilize these monomers with corresponding basic groups in order to release the free base from the salt form of the drug. By requiring this, however, Dr. Flynn explains that the thrust of Müller *et al.*'s disclosure is to incorporate amine functionalities into the polymerized adhesive, to thus create polarity in the adhesive due to the dipole moments exhibited by these amines. All of this is starkly contrasted with the claimed invention hereof, which requires the use of an alkaline consisting essentially of a hydrophobic acrylate polymer.

Dr. Flynn then goes on to specifically consider the effect of utilizing the teachings of Müller *et al.* with the acrylate polymers of this invention. With acrylic acid in particular, the addition of amine groups is shown to have a profound effect on polarity. This not only creates a considerable dipole moment in the molecule, but it also affords strong hydrogen bonding potential. Dr. Flynn thus concludes that the result of the use of Müller *et al.*'s teachings is to render these polymers substantially hydrophilic. This, of course, is precisely contrary to the teachings and objects of the present invention.

It is therefore clear that Müller *et al.* does not suggest to one of ordinary skill in this art that they should produce or utilize a hydrophobic acrylic polymer, as is required hereby. On the contrary, Müller *et al.* teaches away from the use of hydrophobic polymers with the base drug.

Secondly, it is specifically noted that, although Müller *et al.* claims to relate to various types of active components, listing large categories of potential drugs, it is also true that only a single specific drug is disclosed in the

entire Müller *et al.* specification; namely, bopindolol hydrogen malonate. Each of the examples in the specification discloses this drug and no other specific drug. There is clearly no teaching of the present invention in Müller *et al.*, nor any reference therein to a therapeutically effective amount of a drug which is of low molecular weight and liquid at or about room temperature; *i.e.*, a highly plasticizing drug. To the contrary, the only drug disclosed in Müller *et al.* is a salt which is a white solid, is not a plasticizing drug, is not a liquid at room temperature, and in fact has a molecular weight of greater than 380.

Dr. Flynn also recognizes the utter failure of Müller *et al.* to suggest the use of the claimed polymers in conjunction with a highly plasticizing drug. Indeed, he concludes that the concept of utilizing a hydrophobic polymer in conjunction with a highly plasticizing drug is a novel and inventive idea. He reaches this conclusion at least partly because highly plasticizing drugs lack crystallinity, and therefore tend to be highly soluble in many media. They therefore can be too overly soluble in a polar acrylate matrix for efficient delivery; *i.e.*, since the polymer they are placed in is too interactive therewith. This, in turn, lowers their activities at a given concentration, thus reducing their ability to partition onto the skin. Since hydrophobic polymers are not good solvents, they therefore offer higher activities and better partitioning with the skin to drugs which are more polar than they are (essentially all drugs). It is therefore once again clear that the Müller *et al.* patent does not teach the basic subject matter of this invention, and in particular specifically fails to teach the claimed elements thereof.

It is also clear that the mere teaching of the admitted prior use of acrylate-based pressure-sensitive adhesives in transdermal devices by Müller *et al.* does not in

any way amount to a teaching or suggestion of the specific subject matter of the present invention, and particularly not of the claimed subject matter requiring a transdermal product consisting essentially of both a hydrophobic acrylic-based polymer as well as the required highly plasticizing drug as defined herein. In fact, as clearly established by Dr. Flynn's declaration, Müller *et al.* teaches away from both of these components, and is of no use whatsoever in suggesting or teaching the present invention.

The Examiner's final attempt to overcome these deficiencies by combining Müller *et al.* with Buyske clearly is not helpful in this regard. Buyske is basically directed to the transdermal administration of L-deprenyl (selegiline). In particular, this patent claims to have discovered that this drug can be applied for long-term application transdermally without causing skin irritation. Applicants, however, have not claimed that they were the first to have had the concept of transdermally applying selegiline. They are the first, however, to have devised a transdermal device for the application of highly plasticizing drugs, such as selegiline, in a practical and useful adhesive formulation which permits this product to have rare utility. This, however, is neither the subject of Buyske nor of Müller *et al.* Furthermore, even if it were legitimate to combine these references, and applicants do not so admit, this combination would not overcome the clear deficiencies of Müller *et al.* as set forth in detail above. Thus, the combination itself does not teach or suggest the claimed subject matter of the present invention. This rejection should therefore be withdrawn.

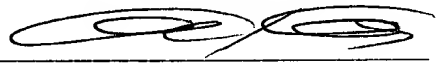
Applicants submit that the latest combination of references asserted by the Examiner in this case is no more relevant than the various other references asserted during the seven-year history of this prosecution. There is no doubt that

the Examiner can continue to search for references of less or at most equal relevance to those which have been cited to date. This serves neither the applicants' nor the public's interest. The prosecution of this application must come to an end at some point. Since the Examiner has not discovered a basis for rejecting the claims in this application which is truly sustainable, applicants again submit that this application is in condition for immediate allowance, and such action is again respectfully solicited. However, in view of the lengthy history of this application and the continued damage done to applicants should this application be further delayed from issuance, it is sincerely requested that the Examiner contact applicants' attorney at 908-654-5000 if any further reasons for rejecting the claims in this application are believed to exist. It is thus hoped that any objections that exist could be overcome quickly so as to permit this application to finally issue.

Finally, if there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: January 13, 2005

Respectfully submitted,

By 

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